

R E M A R K S

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

The specification and the abstract have been reviewed for errors and certain minor editorial corrections are effected. These are believed to be purely editorial in nature and thus not to require extensive discussion.

The claims of the application are amended in a manner to overcome certain objections raised by the Examiner in the recent Official Action and in a manner to most adequately define the subject matter of the present invention.

Thus, claims 1 to 10 inclusive are cancelled without prejudice to the subject matter involved and newly formulated claims 11 to 16 are inserted in their stead. The newly presented claims more specifically define the amounts of the components employed in the composition and method based upon the disclosure in the specification at page 7. The composition claims also now define the presence of the pharmaceutically acceptable additives. Furthermore, the claims as now drawn specify "a synergistically anti-malarial effective amount" of the combination of active ingredients. It is believed that these amendments to the claims will clearly overcome the Examiner's rejection of the claims as failing to adequately define the invention under the provisions of 35 U.S.C. 112 as set forth by the Examiner at page 2 of the recent Official Action. Thus, the Examiner is requested to now reconsider and withdraw this ground of rejection.

The claims are rejected as lacking patentability under the provisions of 35 U.S.C. 103 over Wang et al. (R) and Sethi et al. (S). This ground of rejection is deemed to be untenable and is thus respectfully traversed.

The Wang et al. reference teaches benflumetol and its use as an anti-malarial agent. Sethi et al. teaches arteether and also its anti-malarial activity. The Examiner urges that the individual components are known for the treatment of malaria and that no invention is involved in combining the materials. Applicants respectfully submit that the combination is patentable.

The combination of the anti-malarial agent benflumetol (I) with another anti-malarial agent comprised by the formula II, especially artemether, produces a composition having unexpected and, therefore, surprising properties. The Examiner's attention is directed to the disclosure at page 3 of the specification where it is stated:

"The application of a dosage form comprising the active component benflumetol (I) allows permanent action against malaria. The presence of the second active component (II) in the same dosage form such as artemether ... allows immediate and fast action against protozoa after the outbreak of the disease."

The epidemic malaria is known for its complexity, as this is evident from its multi-stage reproductive cycle preceding its outbreak, and its gravity resulting in an annual death toll of millions in high risk areas of contamination, especially in regions between the tropics of Capricorn and Cancer. Many anti-malarial agents such as artemether or arteether are used for therapy in tropical medicine. However, the large number of fatal cases (steadily increasing each year) clearly shows that chemotherapy must be improved. It is believed that some antimalarial agents

may effectively cure or suppress initial fever attacks but also cause resistance thus allowing recurrent attacks. Other agents are less efficient in the primary stage of the disease but more useful in long term therapy in view of their minor potential for causing resistivity. Their clear disadvantage is their inefficiency to reduce the high fatality caused by initial fever attacks. The administration of agents useful for long term therapy is unsuitable for reducing this risk immediately after the outbreak of the disease.

As to the references cited, even though a general anti-malarial property of the individual chemical compounds according to Refs. R or S is known, this disclosure does not suggest the specific action of those combined agents in therapy. Ref. R especially fails to teach the immediate and fast action against protozoa, especially P. berghei, which is a useful property in the combat against initial fever attacks. Ref. S is deficient in teaching the reduction of recurrent attacks during long term therapy. Both references are also deficient in teaching a dose regimen that component (I) - benflumetol - is administered in excess over component (II) - artemether and derivatives - . In this regard, it is noted that claim 11 has been specified in this regard by incorporation of this excess dosage amount.

The disclosure of the anti-malarial property in both references R and S also fails to suggest some specific properties of the composition recited in the specification at page 6, second paragraph top:

"The ability of the composition to act as an effective and rapid acting anti-malarial agent even against strains of P. berghei known to be extremely resistant against other anti-malarial agents reflects the usefulness of the invention."

Reference is also made to the experimental results reported in the Examples, especially Example 2, which show that the combined agents are surprisingly more efficient as compared to the individual agents. Even if each individual active component present in the claimed composition were known to be effective against malaria, nothing would suggest that the combination of those active components would be more active. The prior art does not teach the individual agents, but clearly fails to teach the idea of combining them. The Examiner's argument has no support from another reference which would suggest just this specific combination of the individual components. Thus, the invention requires more than "mixing together" anti-malarial drugs as the Examiner contends.

Thus, Applicants respectfully submit that the Examiner's rejection based upon the prior art references cited by the Examiner is untenable and the Examiner is respectfully requested to now reconsider and withdraw such rejection.

In order to assist the Examiner in the examination of the application and in order to complete the record of the application, Applicants wish to take this opportunity to bring to the attention of the Examiner information which the Examiner may consider to be material to the examination of the application.

Submitted herewith is a completed form PTO-1449 listing certain publications and attaching copies of said publications.

Initially, it is noted that the publications cited as AL and AT are cited and discussed in the instant specification at pages 1 and 2.

The International Search Report in connection with the corresponding PCT application has been issued and cites one publication which is cited herein as AS.

The final publication cited on the attached completed form PTO-1449 is the World Health Organization publication entitled "Practical Chemotherapy of Malaria". The relevance of this publication lies in the fact that the results reported in the publication date back to an April, 1989 meeting in Beijing. Note particularly the footnote at the bottom of page 124 of the publication. Combinations of benflumetol with artemether are mentioned at page 125 at the bottom and 126 at the top.

This April, 1989 meeting in Beijing was not open to the public and there was no public disclosure of the results presented at that meeting. In view of the non-public nature of the meeting and in view of this lack of public disclosure of the results presented at the meeting, such meeting does not constitute a public disclosure of the subject matter of the present invention and is not, therefore, effective as a reference against the present application.

The Examiner is respectfully requested to take the foregoing information into account in the examination of the present application.

In view of all of the foregoing amendments and remarks, Applicants respectfully submit that each of the grounds of

rejection set forth against the present application has been overcome and that the application is now in condition for allowance; such allowance is solicited.

Respectfully submitted,

YIQING ZHOU ET AL.

BY:


JOHN T. MILLER
Registration No. 21120

JTM/vca
Washington, D. C.
Telephone (202) 371-8850
December 19, 1991